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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/501,223	GUILLON ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *8-11,13-20 and 23-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,12, 21 and 22* is/are rejected.

7)☒ Claim(s) *1-7,12,21 and 22* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 July 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/12/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The Office acknowledges the receipt of Applicant's election and Amendment, filed on 16 July 2007.

Election/Restriction

Applicant elects Group I, claims 1-15, 21 and 22, SEQ ID NO:44, and the mutation species of C27S-K51T-R52L-G79A, with traverse. The traversal is on the grounds that the cited publication by Siderovski *et al.* fails to disclose or make obvious the common technical feature. Applicant's traversal is not persuasive for the following reasons:

As the Applicant indicated in the reply, the common technical feature of the inventions is a HIV-1 Tat protein comprising at least two mutations in the region(s) of amino acid positions 49-57 and/or 88-92. The common technical feature does not require the specific amino acid residues that differentiate between the wild type Tat and the mutant Tat proteins. Siderovski *et al.* (1992) teach a randomly mutatgenized *tat* gene library that expresses Tat proteins with mutations in region 4. See Figure 6. Therefore, the technical feature is not a contribution over the art, and thus, the claimed invention cannot be said to have unity of invention.

The restriction among the different products that may be used in the claimed methods is maintained.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-25 are pending. Claims 8-11, 13-20 and 23-25 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, sequences and species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 16 July 2007.

Claims 1-7, 12, 21 and 22 are examined to the extent that they read on the elected sequence, SEQ ID NO:44, and mutation species.

Information Disclosure Statement

The information disclosure statement (IDS), filed on 12 July 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner. An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

Claim Objections

Claims 1-7, 12, 21 and 22 are objected to for containing non-elected subject matter and grammatical errors. There is no "a" or "an" in front of any noun.

Claim 6 is objected to for missing the word "further" between "it" and "comprises" in the second line of the claim.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 2nd ¶

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-7, 21 and 22 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites "region 4 and/or 5" followed by "domain 5" while it is confusing whether "domain 5" referring to the same amino acid sequence as "region 5." Claim 1 also recites the "RGD motif" of the wild type HIV Tat protein, which is vague and indefinite since the precise amino acid positions of the RGD motif in question are not readily apparent. It is suggested that applicants amend the claim language to recite specific amino acid positions that correspond to the RGD motif.

Furthermore, claims 1-7 recite mutations at various positions in region 4 and/or 5 in the absence of a reference wild type sequence of a specific HIV isolate. Due to the error-prone replication of HIV, there are many quasi species with different nucleotide and amino acid sequences. Especially when insertion or deletion mutations occur during viral replication, the sequences of the quasi species differ substantially from one another that a skilled artisan would not know whether one position number in one strain is referring to the same position in another strain. Therefore, position numbers in the absence of a reference strain number or sequence is vague and indefinite. Furthermore, one skilled in the art would not know what is the wild type amino acid residue at each position because of the existence of so many HIV-1 subtypes and

strains. Claim 1 lacks the recitation of the wild type residues, which is confusing because one would not know how to discern a mutant amino acid from a wild type amino acid at each position when the comparison of the amino acids is not based on a parental isolate sequence.

Claim 6 recites "domain 2" that is indefinite without a definition of specific amino acid residues and position numbers within a specific reference sequence.

Moreover, regarding claims 1, 3, 4 and 6, the phrases "preferably," "capable of," and "advantageously" render the claims indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claims 12, 21 and 22 are rejected for depending from claim 1.

Clarification and/or correction are required.

Claim Rejections - 35 USC § 112, 1st ¶, enablement

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 21 is rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 ¶ 1, the courts have put forth a series of factors (MPEP §2164.01(a)). See, *In re Wands*, 8 USPQ2d 1400, at 1404 (CAFC 1988); and *Ex Parte Forman*, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

Nature of the invention. The claim is drawn to a Tat-protein-based HIV vaccine.

Breadth of the claims. The claimed invention encompasses a large genus of protein vaccines, comprising of any mutant HIV Tat proteins comprising at least two mutations in the region(s) of positions 49-57 and/or 88-92 animal, against any strain of HIV in any subject.

Working examples. The disclosure fails to provide any working embodiments that meet the claimed limitations. No *in vivo* working example of any Tat mutant protein protecting any subject from any strain of HIV is disclosed in the specification.

Guidance in the specification. The disclosure fails to provide adequate guidance pertaining to these considerations: (1) While there is description of construction of DNA coding for the Tat mutants and functional characterization, the

specification does not relate to a vaccine in any example; and (2) There are challenge studies in disease models demonstrating protection or prevention of the HIV. The disclosure fails to provide any working embodiments to enable the full breadth of the claimed invention.

State of the prior art. At the time the invention was made, a pharmaceutical HIV-vaccine comprising a mutant HIV protein is not considered routine in the art. The art of HIV vaccine is highly unpredictable, since HIV replicates rapidly with a high mutational frequency and creates diverse 'quasi-species', which are favored by the Darwinian selective pressures. Therefore, efforts to develop effective treatments and vaccines must overcome the complex evolutionary dynamics in HIV-infected individuals and within affected populations.

Predictability of the art. The immune correlates of viral control in the natural history of HIV disease are unclear and, consequently, the required immune responses to therapeutic vaccination remain elusive (Puls, 2006). A natural immune response, consisting of antibody response and viral-specific $CD8^+$ cellular response as measured in the instant application, is not effective because HIV has evolved a number of evasion strategies: selection for genetic variants that are antigenic escapes variants; inherent resistance to antibody-mediated neutralization; down regulation of major histocompatibility class I molecules from the surface of infected cells by Nef; and destruction of viral-specific $CD4^+$ T helper cells. It is well established in the art that $CD8^+$ cellular responses, or cytotoxic T lymphocyte (CTL) responses select for viral escape variants that are resistant to immune recognition, but the fate of these escape

mutants after transmission to new hosts is unclear. If CTL escape mutations can be reserved after transmission of HIV, HIV escape variants might be propagated in populations. Over time, epitopes targeted by CTL-based vaccines could be lost from circulating virus strains, rendering vaccines that are based on single or consensus strains ineffective. The main problem with HIV vaccines is that there has not been a solution to overcome the enormous sequence heterogeneity of HIV-1 (see Altman *et al.*, 2004; Friedrich *et al.*, 2004; Leslie *et al.*, 2004; and Desrosiers, 2004).

There is little reason to suppose that any currently available vaccine might provide broad protection against HIV infection. Vaccinated monkeys that demonstrated early containment of SHIV and SIV replication with associated benign clinical courses developed abrupt rebounds in viral replication and clinical deterioration. In all of these cases, viruses in the infected monkeys had developed mutations that allowed them to escape recognition by circulating CTL. These mutant viruses became the predominant viruses in the infected animals. The mutant viruses were not controlled by the cellular immune responses and eventually caused immune deterioration and death. Thus, viral escape from CTL may be a general reason for failure with CTL-based vaccines (Letvin, 2005).

Amount of experimentation necessary. The claimed HIV Tat protein vaccine is pure speculation on Applicant's part given that the state of the art of HIV vaccine is highly unpredictable and problematic. There is little guidance in the art and no specific examples of vaccination set forth in the specification. While Applicant is not required to set forth working examples, the specification must set forth sufficient teachings to allow

one to practice the claimed invention, especially when the state of the art teaches that there is no successful HIV vaccine in human trials. There is no evidence that the mutant Tat proteins will actually prevent HIV infection in any subject. When all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to make and use the claimed invention. Thus, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 and 22 are rejected under 35 U.S.C. §102(b) as being anticipated by Garcia *et al.* (1988).

The instant claims are directed to a HIV-1 Tat mutant protein comprising at least two mutations in the region(s) of amino acid positions 49-57 and/or 88-92, and further comprising a mutation replacing any of the cyteines by a serine; and a composition comprising the Tat mutant.

Garcia *et al.* teach a mutant HIV Tat protein with amino acid substitutions C22S, N23T, C27S, C31S, C34S, K50E, R52E, Q54N and R56E. See Figure 1 on page 3144. Thus, the instant invention is anticipated by Garcia *et al.*

Remarks

No claim is allowable.

Applicant is reminded that any amendment must point to a basis in the specification so as not to add new matter. See MPEP §714.02 and §2163.06.

Correspondence

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
12 September 2007

Louise Humphrey, Ph.D.
Assistant Examiner